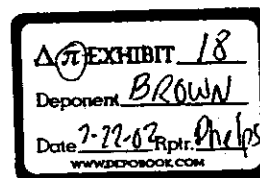


Tab 99



PAPER

An herbal supplement containing Ma Huang-Guarana for weight loss: a randomized, double-blind trial

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OBJECTIVE: To examine in overweight humans the short-term safety and efficacy for weight loss of an herbal supplement containing Ma Huang, Guarana and other ingredients.

DESIGN: An 8 week randomized, double-blind placebo controlled study of a herbal dietary supplement (72 mg/day ephedrine alkaloids and 240 mg/day caffeine).

SUBJECTS: Overweight men and women (body mass index, ≥ 29 and ≤ 35 kg/m²).

MEASUREMENTS: The primary outcome variable was body weight change. Secondary variables included anthropometric, metabolic and cardiovascular changes.

RESULTS: Sixty-seven subjects were randomized to either placebo ($n = 32$) or active Ma Huang/Guarana ($n = 35$). Twenty-four subjects in each group completed the study. Active treatment produced significantly ($P < 0.006$) greater loss of weight ($\bar{X} \pm s.d.$, -4.0 ± 3.4 kg) and fat ($-2.1 \pm 3.0\%$ fat) over the 8-week treatment period than did placebo (-0.8 ± 2.4 kg and $0.2 \pm 2.3\%$ fat). Active treatment also produced greater reductions in hip circumference and serum triglyceride levels. Eight of the 35 actively treated subjects (23%) and none of the 32 placebo-treated control subjects withdrew from the protocol because of potential treatment-related effects. Dry mouth, insomnia and headache were the adverse symptoms reported most frequently by the herbal vs placebo group at the final evaluation visit.

CONCLUSIONS: This herbal mixture of Ma Huang and Guarana effectively promoted short-term weight and fat loss. Safety with long-term use requires further investigation.
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Keywords: alternative medicine; herbal medicine; obesity; clinical trial; ephedra

Introduction

Ma Huang has been used in China for over 5000y as a treatment for asthma and other ailments.^{1,2} The primary active ingredients of Ma Huang (ephedra), are ephedrine alkaloids, sympathomimetic agents. Recently, herbal mixtures of Ma Huang, in combination with Guarana, a source of caffeine, have been marketed in the USA as weight loss agents and many people are now using these products for that purpose.

Factors contributing to the increasing use of such alternative methods for weight control include: the rising pre-

valence of obesity;³ recognition that excessive adiposity increases risk of morbidity and mortality;⁴ and the limited efficacy of conventional weight loss treatments.⁵ Among these alternative methods, preparations that include Ma Huang are among the most popular.²

The Ma Huang/Guarana combination is the herbal counterpart of the well-researched weight loss treatment of ephedrine plus caffeine.^{6–8} Although combinations of ephedrine and caffeine produce weight loss in animals and humans,^{9–14} the efficacy of the herbal combinations for weight loss, to our knowledge, has not been previously evaluated in clinical trials. The issue of adverse effects is also a central question when any agent is used for human weight control management and particularly for herbal preparations that are considered dietary supplements and thereby sold with less regulatory oversight.

The main aim of the present study was to examine the short-term safety and weight-loss promoting effects of an

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herbal supplement containing Ma Huang and Guarana. This investigation is the first reported double-blind placebo-controlled trial of a widely used over-the-counter Ma Huang/Guarana preparation.

Methods

Study design

The study hypothesis was that over an 8 week treatment period a herbal dietary supplement containing Ma Huang and Guarana (ie ephedrine alkaloids and caffeine) promotes significantly greater weight loss than placebo. The primary study outcome was body weight change. Sample size calculations were based on information provided in the National Task Force on the Prevention and Treatment of Obesity report.¹⁵ More than 80% power, at the two-tailed α level of 0.05, would be provided to test the significance of a between-group weight change of 2 kg with a minimum of 30 subjects per group.

After a baseline medical evaluation, subjects were block randomized at visit 0 to active or placebo groups with equal numbers assigned to each group using a random number table and block sizes varying between 2 and 8. Subjects who left the study prior to the first post-randomization visit were replaced with subjects assigned to the same treatment condition by a statistician who was not otherwise involved in the study. All study investigators were blinded. Active or placebo tablets and instruction to exercise moderately and limit intake of dietary fat were provided at visit 0 and at bi-weekly follow-up visits that included measurements of body weight, waist and hip circumference, blood pressure and heart rate. The 0 and 8 week visits also included completion of a symptom questionnaire.

The active preparation was a commercial herbal mixture (Metabolife-356[®], Metabolife Inc., San Diego, CA) containing Ma Huang and Guarana as the main active ingredients. A list of all ingredients with amounts indicated, where this information is not proprietary, is included in the Appendix. Each tablet is labeled as containing 12 mg of total ephedrine alkaloids and 40 mg of caffeine. The total daily amount of ephedrine and caffeine provided in this study were 72 and 240 mg, respectively. The placebo was an identical appearing tablet containing carboxymethylcellulose, micronized silica and alfalfa. An independent laboratory (San Rafael Chemical Services, Salt Lake City, UT) analyzed samples of active and placebo tablets by high pressure liquid chromatography (HPLC) for ephedrine, total ephedrine alkaloids and caffeine.

The study was approved by the Institutional Review Board of St Luke's-Roosevelt Hospital Center and all subjects gave written consent prior to participation.

Subjects

Subjects, recruited by advertisements in local newspapers and flyers, were required to be between 25 and 55 y of age, with body mass index (BMI) ≥ 29 and ≤ 35 kg/m² and to

have been weight stable (± 2.5 kg) for at least 3 months prior to evaluation. Exclusions were pregnancy or nursing within the previous year, diabetes, thyroid, kidney, liver or heart disease, cancer, anemia, high blood pressure, or use of medication other than contraceptives, hormone replacement therapy, or specific allergy preparations.

Treatment

All subjects were advised to limit intake of dietary fat to 30% of calories and to exercise moderately (eg walking 30 min/day, three times a week). Handouts on good eating habits and a progressive walking/exercise program were provided. Active and placebo tablets were supplied in opaque white plastic bottles containing 90 pills/bottle. Subjects were directed to take two tablets, 30 min before each meal, three times a day (6 tablets/day), and to return unused pills, which were counted to determine compliance.

Measurements

Baseline evaluation included medical and nutrition history, a physical examination, blood and urine studies, an electrocardiogram (ECG), and body composition measurements. Blood and urine studies included serum lipids (cholesterol and triglycerides), liver tests, thyroid hormones, glucose, standard electrolytes, ALT, AST and GGT, a complete blood count, and urine analysis (Quest Diagnostic Laboratory, Teterboro, NJ). ECG's were evaluated for four intervals (R-R, P-R, QTc, QRS), QRS amplitude and cardiac rhythm. Body weight and height were measured to the nearest 0.1 kg and 0.5 cm, using a digital scale (Weight Tronix, New York, NY) and stadiometer (Holtain, Crosswell, Wales). Waist and hip circumferences, measured by trained observers at standard anatomical locations,¹⁶ were used as estimates of adipose tissue distribution and cardiovascular risk.¹⁷

Total body fat was assessed by air displacement plethysmography (BodPod[®] Body Composition System, Life Measurement Instruments, Concord, CA) with an error of 0.1% fat.¹⁸ Siri's two-compartment model was used to convert measured body density to percentage fat.¹⁹

Statistical methods

Values are presented in the text as means \pm standard deviation (s.d.) and in the figures as means \pm standard errors (s.e.). All analyses were conducted at the two-tailed 0.05 α -level.

Analysis of study outcomes focused on subjects who completed the study. However, to test for bias due to drop-outs, data was also analyzed by intent-to-treat (ITT) analysis of all randomized subjects, using last observation carried forward (LOCF),²⁰ which conservatively assumes that treatment would not affect variables after the last point of measurement. One placebo subject's final serum triglyceride value, greater than 3 s.d. above the mean, was omitted from the completer analyses. Two-way repeated measures ANOVA

(treatment \times time) was used to compare the pattern of change over time for the herbal treatment vs placebo group for continuous variables, while paired samples, *t*-test was used to examine changes over time within groups, both by SPSS 7.5 (SPSS Inc., Chicago, IL). All data undergoing ANOVA were tested for assumptions of multivariate normality, homogeneity of covariance matrices, and sphericity. Log transformations were applied to data where necessary to meet the first two assumptions while a Greenhouse-Geisser adjustment was used to correct for violations of sphericity.

Results

Baseline subject characteristics

Of 75 subjects evaluated at baseline, eight were disqualified for medical reasons and 67 were randomized, 32 to the placebo group and 35 to the active treatment group (Figure 1). Baseline characteristics did not differ between groups (Table 1). Forty-eight subjects (72%) completed the study with $92 \pm 6\%$ and $94 \pm 5\%$ ($P > 0.3$) pill compliance in the placebo and active treatment subjects respectively.

Herbal analysis

Independent laboratory HPLC analyses detected 1.1 mg caffeine and 0.46 mg total ephedrine alkaloids per placebo tablet and an average of 50.0 (47.0–55.1) mg caffeine (vs 40 mg as labeled), 10.5 (9.7–11.7) mg ephedrine and 12.9 (12.2–13.4) mg total ephedrine alkaloids (vs 12 mg as labeled) per herbal tablet.

Table 1 Baseline demographic characteristics of all randomized subjects

Characteristic	Placebo (n = 32)	Active (n = 35)
Gender		
Men (n)	4	6
Women (n)	28	29
Race n (%)		
White	15 (47%)	18 (51.4%)
African American	10 (31%)	12 (34.3%)
Hispanic	7 (22%)	5 (14.3%)
	($\bar{X} \pm s.d.$)	($\bar{X} \pm s.d.$)
Age (y)	40.0 \pm 9.4	42.2 \pm 8.1
Weight (kg)	88.0 \pm 10.3	90.7 \pm 10.3
Body mass index (kg/m ²)	32.6 \pm 2.9	32.7 \pm 2.7

Treatment effects

Body weight. The mean changes from baseline body weight for all subjects with data at each time point are shown in Figure 2. Comparison of the log transformed weight data showed a significant treatment \times time interaction using a repeated-measures ANOVA (Greenhouse-Geisser adjusted $P = 0.001$). Using weight at baseline as a covariate, the treatment \times time interaction was still significant (Greenhouse-Geisser adjusted $P = 0.002$). Of subjects completing the study, there was a significant decrease in weight in the herbal treatment group (-4.0 ± 3.4 kg or 3.5 % of baseline, Greenhouse-Geisser adjusted $P < 0.001$) but not in the placebo group (-0.8 ± 2.4 kg or 0.09% of baseline, Greenhouse-Geisser adjusted $P = 0.07$, Table 2).

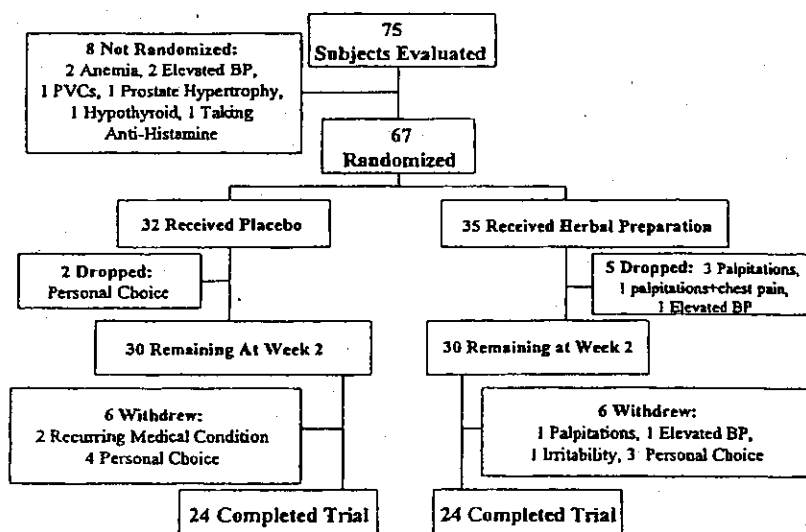


Figure 1 Disposition of subjects enrolled in the study.

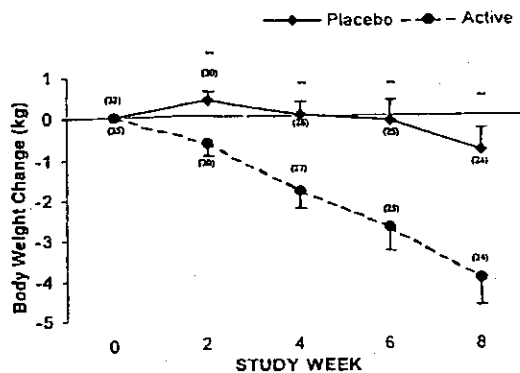


Figure 2 Change in body weight (kg) over the 8 week study period for all subjects in active treatment and placebo groups. The plotted values represent the mean \pm s.e. (n) at each time point. Triangles with solid lines depict the placebo group and circles with dashed lines depict the treatment group.

Body fat. Changes were significantly greater for body fat and percentage body fat in the active group (-3.5 ± 3.3 kg, $P < 0.001$ and $-2.1 \pm 3.0\%$, $P = 0.002$) than in the placebo group (-0.7 ± 2.9 kg, $P = 0.282$ and $0.2 \pm 2.3\%$, $P = 0.725$, Table 2).

Anthropometric dimensions. There were significantly greater reductions in waist and hip circumferences

($P = 0.050$, $P < 0.001$, respectively) in the herbal group (-3.4 ± 5.0 cm, $P = 0.003$ and -4.7 ± 4.2 cm, $P < 0.001$) than the placebo group (-0.8 ± 3.8 cm, $P = 0.300$ and -0.4 ± 2.4 cm, $P = 0.397$; Table 2).

Cardiovascular end-points. The only statistically significant effect on serum lipids was the decrease in serum triglyceride levels, which was greater ($P = 0.007$) in the active (-0.2 ± 0.4 mmol/l, $P = 0.057$), vs the placebo group (0.1 ± 0.3 mmol/l, $P = 0.056$; Table 3).

The small mean increase in serum glucose levels in the active treatment group (0.2 ± 0.4 mmol/l ($P = 0.029$)) was significantly ($P = 0.006$) larger than the change in the control group (-0.1 ± 0.4 mmol/l, $P = 0.095$; Table 3). No subject in either group had end-of-study serum glucose levels in the clinically abnormal range.

Mean systolic and diastolic blood pressure did not differ between groups at any time point nor were they different from baseline in either group at the end of the study (Table 2). When the rise over baseline was compared for all subjects at each time point, mean systolic blood pressure was significantly ($P = 0.025$) greater only at week 6 in the active treatment group (4.1 ± 12.3 mmHg) than the control group (-2.6 ± 8.3 mmHg), Figure 3). Repeated measures analysis of completers, however, showed that the variability of the change in blood pressure was constant within subjects over groups and the between-group effect was not significant ($P = 0.090$) unless weight loss was used as a covariate ($P = 0.022$). The changes from baseline in diastolic blood

Table 2 Physical values for subjects who completed the 8 week study protocol*

Measure	Study period	Group		P ^c
		Placebo $\bar{x} \pm$ s.d. (P-value) ^a	Active $\bar{x} \pm$ s.d. (P-value) ^a	
Body weight (kg)	Baseline	87.1 \pm 10.1	91.6 \pm 11.1	< 0.001
	Final	86.3 \pm 10.4	87.6 \pm 10.5	
	Change	-0.8 \pm 2.4 (0.07)	-4.0 \pm 3.4 (< 0.001)	
Body fat mass (%)	Baseline	41.2 \pm 5.1	40.4 \pm 8.0	0.006
	Final	41.4 \pm 5.4	38.3 \pm 8.8	
	Change	0.2 \pm 2.3 (0.725)	-2.1 \pm 3.0 (0.002)	
Waist circumference (cm)	Baseline	98.4 \pm 8.9	99.1 \pm 8.2	0.050
	Final	97.6 \pm 8.8	95.7 \pm 7.1	
	Change	-0.8 \pm 3.8 (0.300)	-3.4 \pm 5.0 (0.003)	
Hip circumference (cm)	Baseline	114.0 \pm 5.1	115.9 \pm 8.2	< 0.001
	Final	113.5 \pm 5.6	111.1 \pm 7.8	
	Change	-0.4 \pm 2.4 (0.397)	-4.7 \pm 4.2 (< 0.001)	
Systolic blood pressure (mmHg)	Baseline	115.5 \pm 9.2	113.2 \pm 8.3	0.284
	Final	112.6 \pm 8.9	113.3 \pm 9.0	
	Change	-3.0 \pm 9.7 (0.150)	0.1 \pm 10 (0.952)	
Diastolic blood pressure (mmHg)	Baseline	76.4 \pm 8.4	75.0 \pm 7.9	0.904
	Final	75.2 \pm 7.3	74.1 \pm 9.0	
	Change	-1.2 \pm 8.1 (0.471)	-0.9 \pm 8.6 (0.605)	
Heart rate (beats/min)	Baseline	73.4 \pm 8.9	67.2 \pm 4.9	< 0.001
	Final	71.7 \pm 8.0	74.1 \pm 7.5	
	Change	-1.7 \pm 6.3 (0.211)	6.9 \pm 6.9 (< 0.001)	

*Treatment was an herbal supplement containing 72 mg ephedra and 240 mg caffeine/day.

^aP-values for within-group change from baseline compared by paired samples t-test (Greenhouse-Geisser adjusted where appropriate).

^cMean changes of subjects in treatment (n = 24) vs placebo (n = 24) groups who completed the study compared by independent samples t-test (Greenhouse-Geisser adjusted where appropriate).

Table 3 Serum values for subjects who completed the 8 week study protocol*

		Serum levels ^a				P ^c
Study period		Placebo Mean \pm s.d. (P-value) ^b		Active Mean \pm s.d. (P-value) ^b		
		(mmol/l)	(mg/dl)	(mmol/l)	(mg/dl)	
Cholesterol	Baseline	5.3 \pm 1.2	203.5 \pm 45.2	4.7 \pm 0.9	181.3 \pm 36.0	0.335
	Final	5.3 \pm 1.3	205.5 \pm 51.4	4.6 \pm 1.0	176.9 \pm 37.9	
	Change	0.0 \pm 0.7 (0.713)	2.0 \pm 26.3	-0.1 \pm 0.5 (0.254)	-4.4 \pm 18.3	
HDL-Cholesterol	Baseline	1.3 \pm 0.3	49.8 \pm 13.1	1.3 \pm 0.4	51.1 \pm 14.9	0.957
	Final	1.4 \pm 0.4	52.6 \pm 15.2	1.4 \pm 0.4	53.8 \pm 13.9	
	Change	0.1 \pm 0.2 (0.160)	2.9 \pm 9.7	0.1 \pm 0.2 (0.100)	2.7 \pm 7.9	
LDL-Cholesterol	Baseline	3.4 \pm 0.9	132.4 \pm 36.8	2.9 \pm 0.7	111.4 \pm 26.4	0.845
	Final	3.4 \pm 1.1	129.5 \pm 44.2	2.8 \pm 0.8	107.3 \pm 32.8	
	Change	0.1 \pm 0.6 (0.545)	-2.9 \pm 23.1	-0.1 \pm 0.4 (0.261)	-4.0 \pm 17.2	
Triglycerides	Baseline	1.0 \pm 0.6	92.6 \pm 53.3	1.0 \pm 0.6	93.6 \pm 52.8	0.007
	Final	1.1 \pm 0.5	101.1 \pm 45.8	0.8 \pm 0.4	77.9 \pm 35.2	
	Change	0.1 \pm 0.3 (0.056)	8.5 \pm 29.2	-0.2 \pm 0.4 (0.057)	-15.7 \pm 38.3	
Glucose	Baseline	4.9 \pm 0.5	88.6 \pm 8.4	4.6 \pm 0.04	83.4 \pm 6.7	0.006
	Final	4.7 \pm 0.5	86.1 \pm 8.5	4.8 \pm 0.03	87.2 \pm 6.4	
	Change	-0.1 \pm 0.4 (0.095)	-2.4 \pm 6.9	0.2 \pm 0.4 (0.029)	3.8 \pm 8.1	

*Twenty-four subjects group completed the study. Treatment was a herbal supplement containing 72 mg ephedra and 240 mg caffeine/day.

^bP-value for within-group change from baseline compared by paired samples t-test.

^cMean changes in treatment vs placebo groups for subjects who completed the 8 week study compared by independent samples t-test.

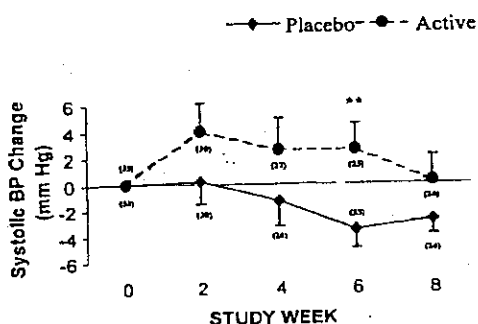


Figure 3 Change in systolic blood pressure (BP, mmHg) over the 8 week study period for all subjects in active treatment and placebo groups. The plotted values represent the mean \pm s.e. (n) at each time point. Triangles with solid lines depict the placebo group and circles with dashed lines depict the treatment group.

pressure were not significant in either group over time or between groups at each time point, even after controlling for weight loss.

Heart rate at week 8 was significantly ($P < 0.001$) increased over baseline in the active treatment group (6.9 ± 6.9 beats/min) compared with the control group (-1.7 ± 6.3 beats/min; Table 2). The within-group changes in heart rate were also significant for the herbal treatment group ($P < 0.001$) but not the placebo group ($P = 0.211$).

All measured group mean amplitudes and intervals were within their respective normal ranges at baseline and there were no significant within or between-group ECG changes

over the treatment period except for the R-R interval. The R-R interval (lead 2) decreased significantly ($P = 0.027$) in length (-0.057 ± 0.11 s) in the active treatment group and this was also significantly different ($P = 0.047$) from the change in the placebo group ($+0.007 \pm 0.10$ s, $P = 0.724$). No ectopic beats or arrhythmias were observed either at baseline or at week 8 on the standard ECG.

Blood chemistries. There were no significant within-group changes from baseline for electrolytes, ALT, AST or GGT in the placebo group. In the active treatment group, both ALT and AST decreased significantly from baseline (-4.2 ± 10 IU/l, $P = 0.050$ and -2.2 ± 5.2 IU/l, $P = 0.051$, respectively) while GGT and electrolytes remained unchanged.

ITT analysis of treatment outcomes. To avoid possible bias due to subjects who were lost to follow-up, ITT analysis was performed with all missing data imputed by carrying forward the last previous measurement to the final observation. This very conservative treatment of the data resulted in changes in the magnitude of differences between groups, but did not change the statistical significance of any of the treatment outcomes (Table 4).

Adverse effects. Adverse effects are presented in Figure 1 and Table 5. Five of the 35 subjects (14%) taking the active preparation left the study prior to the first follow-up visit due to potentially treatment-related adverse effects (Figure 1). One of these subjects was found to have elevated blood pressure (140/90 mmHg, systolic/diastolic). The other four reported palpitations with ($n = 1$) or without ($n = 3$) chest pain within a few days of beginning treatment. Follow-up

Table 4 Physical and serum values for all randomized subjects*

	Placebo		Active		P ^c
	Mean \pm s.d. (P-value) ^b		Mean \pm s.d. (P-value) ^b		
Body weight (kg)	- 0.7 \pm 2.2 (0.074)		- 2.7 \pm 3.4 (< 0.001)		0.007
Fat mass (%)	0.2 \pm 2.0 (0.581)		- 1.5 \pm 2.7 (0.003)		0.006
Waist circumference (cm)	- 0.4 \pm 3.6 (0.519)		- 2.2 \pm 4.7 (0.008)		0.079
Hip circumference (cm)	- 0.3 \pm 2.3 (0.497)		- 3.6 \pm 4.0 (0.007)		< 0.001
Systolic blood pressure (mmHg)	- 1.8 \pm 9.9 (0.316)		2.1 \pm 11.3 (0.298)		0.149
Diastolic blood pressure (mmHg)	- 1.5 \pm 8.1 (0.312)		0.1 \pm 8.2 (0.930)		0.416
Heart rate (beats/min)	- 0.9 \pm 5.8 (0.372)		4.7 \pm 6.8 (< 0.001)		< 0.001
Serum levels	mmol/l	mg/dl	mmol/l	mg/dl	
Cholesterol	0.0 \pm 0.7 (0.711)	2.0 \pm 26.3	- 0.1 \pm 0.4 (0.252)	- 3.0 \pm 15.2	0.343
HDL-cholesterol	0.0 \pm 0.2 (0.159)	2.2 \pm 8.6	0.0 \pm 0.2 (0.100)	1.9 \pm 6.6	0.853
LDL-cholesterol	- 0.1 \pm 0.5 (0.543)	- 2.2 \pm 20.3	- 0.1 \pm 0.3 (0.259)	- 2.8 \pm 14.3	0.901
Triglycerides	0.2 \pm 0.5 (0.057)	16.2 \pm 45.4	- 0.1 \pm 0.3 (0.058)	- 10.7 \pm 32.4	0.007
Glucose	- 0.1 \pm 0.3 (0.095)	- 1.9 \pm 6.1	0.1 \pm 0.4 (0.030)	2.6 \pm 6.9	0.007

*Intent-to-treat analysis. Treatment was a herbal supplement containing 72 mg ephedra and 240 mg caffeine/day.

^bP-value for within-group change from baseline compared by paired samples t-test.^cMean changes in treatment vs placebo groups compared by independent samples t-test.

Table 5 Symptoms reported by subjects at the 8 week final evaluation visit

	Placebo	Active
Number of subjects	24	24
Symptom		
Central nervous system		
Irritability	3	5
Dizziness	1	3
Insomnia	9	13
Anxiety	6	6
Headache	4	7
Blurred vision	2	1
Poor concentration	3	2
Total	28	37
Cardiovascular		
Palpitations	1	1
Total	1	1
Gastrointestinal		
Constipation	4	2
Diarrhea	1	2
Upset stomach	2	0
Heart burn	2	4
Nausea	0	2
Total	9	10
Other		
Dry mouth	4	11
Chest pain	1	1

ECGs showed no significant abnormalities in any of these subjects. After week 2, six additional subjects (17%) in the active treatment group withdrew from the study, one due to increased blood pressure, one reporting increased palpitations, one reporting extreme irritability and two for personal reasons.

Eight subjects, of 32 enrolled (25%), withdrew from the placebo group, all for reasons unrelated to the study protocol (two quit, one moved away, two other commitments, one missed 2 weeks of medication due to travel, one recurring

urinary tract infection, one recurring menopausal symptoms). Altogether, there were eight (two physician-removed, six self-removed) potentially treatment-related dropouts (23%) in the active group and none in the placebo group.

Symptoms reported by subjects at the final evaluation are grouped in Table 5 into four categories: central nervous system (CNS), cardiovascular, gastrointestinal and other. The CNS category had the greatest difference between active and placebo treatment groups while individual symptoms with greatest differences were dry mouth (11 vs 4), insomnia (13 vs 9) and headache (7 vs 4) for active and placebo groups, respectively.

Discussion

The principal finding of this study was that an herbal preparation with Ma Huang and Guarana as the main active ingredients, administered with diet and exercise counseling, promoted significant loss of body weight and fat in overweight subjects beyond that observed in similarly counseled placebo-treated subjects. The weight loss and additional beneficial responses observed in actively treated subjects were accompanied by stimulatory effects characteristic of ephedrine and caffeine.^{21,22} However, the possibility that some of the other ingredients contained in the product contributed to these and other effects cannot be excluded. Eight of the 35 subjects in the herbal treatment group withdrew from the study for symptoms such as palpitations and those remaining reported a higher rate of side effects than did subjects in the placebo group, although no subject had any serious or lasting negative side effects.

Body weight effects

Results from the present study of a herbal preparation extend parallel findings observed in humans and animals treated

with synthetic ephedrine-caffeine combinations. Malchow-Moller and colleagues in 1981¹⁴ demonstrated that obese subjects assigned to a hypocaloric diet for 12 weeks had 4.0 kg greater weight-loss when given ephedrine (180 mg/day) and caffeine (300 mg/day) than with placebo. A subsequent 24-week trial of ephedrine (60 mg/day) and caffeine (600 mg/day) along with an assigned low-energy (4.2 MJ/day) diet produced a 3.8 kg greater weight loss in obese subjects than did placebo.¹³ In the only study that did not include energy restriction, Daly and colleagues observed significantly greater weight loss over 8 weeks (2.2 kg) in obese subjects treated with ephedrine (75-150 mg/day), caffeine (150 mg/day), and aspirin (330 mg/day) than those given placebo (0.7 kg).²² The weight loss due to treatment observed in the present study (4 kg) is consistent with these earlier reports.

Ephedrine-caffeine combinations promote weight loss by reducing food intake^{11,23} as well as by increasing thermogenesis.^{10,12,23,24} Ephedrine's thermogenic activity has also been observed in isolated rat brown adipocytes where it mimics norepinephrine β -adrenergic effects.⁹

The effect of methylxanthines, such as caffeine, to potentiate the thermogenic effect of ephedrine is thought to be due to reduced negative feedback inhibition mechanisms that suppress catecholamine release.²⁵ These include activation of presynaptic α -2 adrenoceptors, release of prostaglandins and adenosine into synaptic junctions, and increased activity of cellular phosphodiesterase enzyme activity, which would increase degradation of cyclic AMP. Astrup and colleagues have also shown that the effects of specific doses of ephedrine and caffeine (60 and 600 mg/day, respectively) produce synergistic thermogenic effects compared to the effects of either agent alone.²³ The increased weight loss of subjects taking a Ma Huang/Guarana combination containing ephedrine and caffeine may thus be a consequence of both increased energy expenditure and decreased energy intake.

In the present study, there were significant reductions in percentage body fat, waist and hip circumferences and serum triglycerides that paralleled weight loss in the treatment group. Additional between-group differences in serum lipid levels might be expected in a longer term study.

Cardiovascular effects

The small and transitory increase in systolic blood pressure in the herbal treatment group here is consistent with the acute²³ and transitory²² increases previously described with ephedrine/caffeine treatment. Astrup and colleagues reported increases of 5-7 mmHg more than placebo, 3 h after administration of each of three combinations of ephedrine/caffeine (10/200, 20/100 and 20/200 mg) to healthy, lean subjects.²³ Acute effects of Ma Huang (19.4 mg ephedrine) were found to be variable in normotensive, healthy adults, with 2/12 having significantly increased (5-7 mmHg) and 2/12 having significantly decreased (4-9 mmHg) mean 12 h systolic blood pressures.⁶

Longer term studies (6 weeks to 6 months) of ephedrine-caffeine mixtures that produced weight losses report either no change^{14,22} in blood pressure or decrease from baseline.^{23,27-29} Astrup's study of 180 obese subjects showed that during 24 weeks of treatment with ephedrine and caffeine (60/600 mg/day) plus a hypoenergetic diet, both systolic and diastolic blood pressures declined more slowly than those of subjects treated with diet alone. By week 12, however, both were significantly lower than baseline and at no point were they statistically different from those of the group treated with diet alone.⁷ Breum's 15-week study²⁷ of 50 obese subjects treated with ephedrine/caffeine (60/600 mg/day) and Greenway's 6 month study²⁹ of 25 obese subjects treated with ephedrine/caffeine (75/600 mg/day) also showed improvements in blood pressure with weight loss. Greenway and colleagues calculated that, per 1% of weight loss with ephedrine/caffeine treatment, blood pressure decreased by 0.65/0.18 mmHg (systolic/diastolic).²⁹ If results from chronic Ma Huang/Guarana treatment are similar to those for ephedrine/caffeine, beneficial effects on blood pressure with greater weight loss would be expected. Withdrawal of two subjects from our study due to acutely increased blood pressures (140/90 mmHg), however, suggests that individuals should be aware of this possibility prior to potential decreases secondary to weight loss.

Increases in heart rate following acute²³ treatment with ephedrine/caffeine are consistent with the known stimulatory effects of this combination on energy expenditure.^{10,23} In a study of acute effects of Ma Huang (19.4 mg ephedrine, 4.9 mg pseudoephedrine, and 1.2 mg methylephedrine), White and colleagues, using ambulatory monitors, found that six of 12 participants had statistically, but nonclinically significant increases in mean 12 h heart rate.⁶ Chronic treatments with ephedrine/caffeine have reported either no significant effect on heart rate²² or a slower rate of decrease with weight loss than placebo-treated subjects.⁷

Maximal cardiovascular effects of ephedrine and caffeine are usually observed within several hours of ingestion²³ and during the early phase of treatment.^{13,23,26,27} Dulloo and Stock have suggested that tachyphylaxis limits the undesirable side-effects of ephedrine/caffeine treatment, while the weight loss effects are persistent with chronic treatment.²⁹ The present study protocol was designed to initiate and maintain subjects on a relatively high intake of Ma Huang-Guarana. A more gradual transition from lower to higher treatment dose might have resulted in fewer cardiovascular side effects by allowing time for development of tachyphylaxis.²² Additional Ma Huang-Guarana studies are required to fully characterize the short and long-term cardiovascular effects of these widely available preparations.

The small, but statistically significant, increase in fasting serum glucose that occurred in the active treatment group of this study does not agree with the lack of effect seen in previous 8 week studies of ephedrine/caffeine combinations in humans²² and monkeys.⁴ Serum glucose levels have been reported, however, to be elevated 30 min after ingestion of

10, 20 or 40 mg of synthetic ephedrine with return to baseline within 3 h.²¹ These reports suggest that the elevation in serum glucose in the present study could be an acute response to ingestion of tablets by some subjects prior to blood sampling. Future studies should ensure that fasting blood samples are taken prior to ingestion of the herbal preparation to answer this question. Alternatively, the Guarana component or other ingredients, might have contributed to elevated plasma glucose levels. Guarana extracts have been shown to increase serum glucose levels and decrease liver glycogen content of mice.³¹ While the serum glucose effects were relatively small in magnitude in our nondiabetic patients, the response of obese diabetic patients to this and to similar products needs to be established.

Adverse effects

Use of Ma Huang is controversial. Some authors have described it as 'unsafe'^{2,32} and numerous anecdotal reports of adverse effects attributed to its consumption³³ led the Federal Drug Administration (FDA) to propose a rule that would define a level of ephedrine alkaloids in supplements and require warning statements on product labels to restrict use to no more than 7 days.³⁴ Subsequent review of that proposal, however, led the Government Accounting Office to declare that the evidence for the FDA recommendation was inadequate, citing the need for additional information.³⁵

No subject had any serious or lasting adverse event in this relatively short-term and small-scale study. The measured (ie heart rate, systolic blood pressure and serum glucose elevations) and self-reported (ie palpitations, dry mouth and insomnia) adverse or undesirable effects observed in the present study could be anticipated based on earlier ephedrine/cafeine studies and are consistent with the sympathomimetic action of Ma Huang.

It is useful to compare the results observed in the present study of a Ma Huang/Guarana combination with those reported for sibutramine, a widely used prescription drug currently approved by the Federal Drug Administration (FDA) for the treatment of obesity. Sibutramine, described as 'well tolerated' by Bray *et al*,³⁶ promotes comparable weight loss,³⁶⁻³⁸ increases heart rate to a similar extent^{36,37,39} and acutely increases plasma glucose.⁴⁰ As with Ma Huang/Guarana, commonly reported side effects of sibutramine, other than effects on appetite, include dry mouth and insomnia, postulated to result from stimulation of sympathetic nervous system activity.³⁶ One potentially important difference, however, is that while the statistically significant increase in systolic blood pressure was only transitory in the present study of Ma Huang/Guarana, increased blood pressure persists throughout treatment with sibutramine.³⁶

The present carefully conducted double-blind, randomized, placebo-controlled study identified clear benefits (weight loss, fat loss, reduction of waist and hip circumferences and lowered triglyceride levels) as well as potential

risks (self-reported palpitations, increased serum glucose and transitory increases in systolic blood pressure) from consumption of Ma Huang/Guarana. The critical question for any treatment is what risks are tolerable for the associated benefits. An additional question for herbal supplements is whether the risk/benefit ratio should be greater for an over-the-counter treatment that can be purchased by medically unsupervised individuals vs a medication that is provided for use only under physician supervision. Additional long-term randomized, placebo-controlled clinical studies to address the safety and efficacy of these and other herbal supplements are clearly needed to provide the basis for answers to these questions. One long-term trial is currently in progress.

Conclusion

The present study demonstrated a significant weight and fat loss effect of an herbal Ma Huang-Guarana mixture in healthy overweight subjects. The tested product also produced several untoward side effects, leading some actively treated subjects to withdraw from the study. Additional long-term studies are needed to elucidate effects of chronic treatment.

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References

- 1 Chen KK. A comparative study of synthetic and natural ephedrine. *J Pharmac Exp Ther* 1929; 34: 237-258.
- 2 Tyler VE. *The honest herbal*, 3rd edn, Hayworth Press: Binghamton, Hayworth Press; New York; 1993.
- 3 Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL. Increasing prevalence of overweight among US adults. The National Health and Nutrition Examination Surveys, 1960 to 1991. *JAMA* 1994; 272: 205-211.
- 4 Han TS, Richmond P, Avenell A, Lean ME. Waist circumference reduction and cardiovascular benefits during weight loss in women. *Int J Obes Relat Metab Disord* 1997; 21: 127-134.
- 5 Heymsfield SB, Allison DB, Vasselli JR, Pietrobello A, Greensfield D, Nunez C. *Garcinia cambogia* (hydroxycitric acid) as a potential antiobesity agent. A randomized clinical trial. *JAMA* 1998; 280: 1596-1600.
- 6 White LM, Gardner SE, Gurley BJ, Marx MA, Wang PL, Estes M. Pharmacokinetics and cardiovascular effects of ma-huang (*Ephedra sinica*) in normotensive adults. *J Clin Pharmacol* 1997; 37: 116-122.
- 7 Astrup A, Breum L, Toubro S, Hein P, Quaade F. The effect and safety of an ephedrine/cafeine compound compared to ephedrine, caffeine and placebo in obese subjects on an energy restricted diet. A double-blind trial. *Int J Obes Relat Metab Disord* 1993; 16: 269-277.

- 8 Betz JM, Gay ML, Mossoba MM, Adams S. Chiral gas chromatographic Determination of ephedrine-type alkaloids in dietary supplements containing Ma Huang. *J AOAC Int* 1997; 80: 303-315.
- 9 Bukowiecki L, Jahjah L, Follea N. Ephedrine, a potential slimming drug, directly stimulates thermogenesis in brown adipocytes via beta-adrenoreceptors. *Int J Obes* 1982; 6: 343-350.
- 10 Dulloo AG, Miller DS. The thermogenic properties of ephedrine/methylxanthine mixtures: human studies. *Int J Obes* 1986; 10: 467-481.
- 11 Dulloo AG, Miller DS. Reversal of obesity in the genetically obese *fafa* Zucker rat with an ephedrine/methylxanthines thermogenic mixture. *J Nutr* 1987; 117: 383-389.
- 12 Dulloo AG, Miller S. The thermogenic properties of ephedrine/methylxanthine mixtures: animal studies. *Am J Clin Nutr* 1986; 43: 388-394.
- 13 Toubro S, Astrup A, Breum L, Quaade F. Safety and efficacy of long-term treatment with ephedrine, caffeine, and ephedrine/caffeine mixture. *Int J Obes Relat Metab Disord* 1993; 17: S69-S72.
- 14 Malchow-Moller A, Larsen S, Hey H, Stokholm KH, Junl E, Quaade F. Ephedrine as an anorectic: the story of the 'Elsinore pill'. *Int J Obes* 1981; 5: 183-187.
- 15 National Task Force on the Prevention and Treatment of Obesity. Long term pharmacotherapy in the management of obesity. *JAMA* 1996; 276: 1907-1915.
- 16 Lohman TG. *Advances in body composition assessment*. Human Kinetics: Champaign, IL; 1992.
- 17 Pi-Sunyer FX. Short-term medical benefits and adverse effects of weight loss. *Ann Intern Med* 1993; 119: 722-726.
- 18 Dempster R, Aitkens S. A new air displacement method for determination of human body composition. *Med Sci Sports Exerc* 1995; 27: 1692-1697.
- 19 Siri WE. Body composition from fluid spaces and density: analysis of methods. In: *Techniques for measuring body composition*. NAS: Washington, DC; 1961. pp 223-248.
- 20 Niklson IA, Reimitz PE, Sennel C. Factors that influence the outcome of placebo-controlled antidepressant clinical trials. *Psychopharmac Bull* 1997; 33: 41-51.
- 21 Astrup A, Toubro S, Cannon S, Hein P, Madsen J. Thermogenic, metabolic, and cardiovascular effects of a sympathomimetic agent, ephedrine. *Curr Ther Res* 1990; 48: 1087-1100.
- 22 Daly PA, Krieger DR, Dulloo AG, Young JB, Landsberg L. Ephedrine, caffeine and aspirin: safety and efficacy for treatment of human obesity. *Int J Obes Relat Metab Disord* 1993; 17: S73-S78.
- 23 Astrup A, Toubro S, Cannon S, Hein P, Madsen J. Thermogenic synergism between ephedrine and caffeine in healthy volunteers: a double blind placebo-controlled study. *Metabolism* 1991; 40: 323-329.
- 24 Ramsey JJ, Colman RJ, Swick AG, Kemnitz JW. Energy expenditure, body composition, and glucose metabolism in lean and obese rhesus monkeys treated with ephedrine and caffeine. *Am J Clin Nutr* 1998; 68: 42-51.
- 25 Dulloo AG. Ephedrine, xanthines and prostaglandin-inhibitors; actions and interactions in the stimulation of thermogenesis. *Int J Obes Relat Metab Disord* 1993; 17: S35-S40.
- 26 Pasquali R, Casimirri F. Clinical aspects of ephedrine in the treatment of obesity. *Int J Obes Relat Metab Disord* 1993; 17: S65-S68.
- 27 Breum L, Pedersen JK, Ahlstrom F, Frimodt-Moller J. Comparison of an ephedrine/caffeine combination and dexfenfluramine in the treatment of obesity. A double-blind multi-centre trial in general practice. *Int J Obes Relat Metab Disord* 1994; 18: 99-103.
- 28 Svendsen TL, Ingerslev J, Mork A. [Is Letigen contraindicated in hypertension? A double-blind, placebo controlled multipractice study of letigen administered to normotensive and adequately treated patients with hypersensitivity]. *Ugeskr Laeger* 1998; 160: 4073-4075.
- 29 Greenway FL, Ryan DH, Bray GA, Rood JC, Tucker EW, Smith SR. Pharmaceutical cost savings of treating obesity with weight loss medications. *Obes Res* 1999; 7: 523-530.
- 30 Dulloo AG, Stock MJ. Editorial. *Int J Obes Relat Metab Disord* 1993; 17: S1-S2.
- 31 Miura T, Tataru M, Nakamura K, Suzuki I. Effect of Guarana on exercise in normal and ephedrine-induced glycogenolytic mice. *Biol Pharm Bull* 1998; 21: 646-648.
- 32 Klepser TB, Klepser ME. Unsafe and potentially safe herbal therapies. *Am J Health Syst Pharm* 1999; 56: 138.
- 33 Anonymous. Adverse events associated with ephedrine-containing products—Texas, December 1993–September 1995. *Morb Mortal Wkly Rep* 1996; 45: 689-693.
- 34 62 Federal Register 30678.
- 35 GAO/HEHS/GGD-99-90. Dietary supplements: uncertainties in analyses underlying FDA's proposed rule on ephedrine alkaloids.
- 36 Bray GA, Blackburn GL, Ferguson JM, Greenway FL, Jain AK, Mendel CM, Mendels J, Ryan DH, Schwartz SL, Scheinbaum ML, Seaton TB. Sibutramine produces dose-related weight loss. *Obes Res* 1999; 7: 189-198.
- 37 Hanotin C, Thomas F, Jones SP, Leutenegger E, Drouin P. Efficacy and tolerability of sibutramine in obese patients: a dose-ranging study. *Int J Obes Relat Metab Disord* 1998; 22: 32-38.
- 38 Weintraub J, Rubio A, Golik A, Byrne L, Scheinbaum ML. Sibutramine in weight control: a dose-ranging, efficacy study. *Clin Pharmac Ther* 1991; 50: 330-337.
- 39 Hanotin C, Thomas F, Jones SP, Leutenegger E, Drouin P. A comparison of sibutramine and dexfenfluramine in the treatment of obesity. *Obes Res* 1998; 6: 285-291.
- 40 Hansen DL, Toubro S, Stock MJ, Macdonald IA, Astrup A. Thermogenic effects of sibutramine in humans. *Am J Clin Nutr* 1998; 68: 1180-1186.

Appendix

Reported composition of Metabolife-356 (Metabolife Inc., San Diego, CA): Vitamin E, 6 IU; magnesium protein chelate, 75 mg; zinc chelate, 5 mg; chromium picolinate, 75 µg; proprietary blend, 728 mg; Guarana, 40 mg; Ma Huang, 12 mg;

bee pollen; ginseng (root); ginger (root); damiana (leaf); sarsaparilla (root); goldenseal (aerial part); nettles (leaf); bovine complex; gotu kola; lecithin; spirulina algae; royal jelly; and other ingredients (binders, etc), methacel, silica, croscarmellose sodium and magnesium stearate.